Impact of rosiglitazone meta-analysis on use of glucose-lowering medications

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ABSTRACT

Background: In May 2007 Nissen and Wolski reported the results of a meta-analysis showing an association between use of rosiglitazone and increased risk of myocardial infarction (*N Engl J Med* 2007;356[24]:2457–2471). Rosiglitazone is an insulin-sensitizing agent used to control blood glucose levels in patients with type 2 diabetes. Subsequent analyses provided evidence that the meta-analysis led to a decline in new and prevalent use of rosiglitazone. We sought to evaluate the impact of the meta-analysis on patterns of use of glucose-lowering drugs and patterns of initiation, cessation and switching of drug therapy, and to estimate the impact in relation to other predictors of initiation and cessation of rosiglitazone.

Methods: We used an interrupted time series analysis to test the impact of the meta-analysis on monthly utilization of glucose-lowering drugs for the 4.3 million residents of the province of British Columbia. We used multivariate logistic regression with generalized estimating equations to test predictors of initiation and cessation of rosiglitazone, including the influence of microvascular and macrovascular comorbidities, before and after the meta-analysis.

Results: A comparison of predicted and observed utilization for November 2007 showed that use of rosiglitazone declined by 40% (95% confidence interval 39%–42%), whereas use of pioglitazone, insulin and sulfonylureas increased. The presence of macrovascular comorbidities strengthened both the negative impact of the meta-analysis on initiation of rosiglitazone therapy and the positive impact of the meta-analysis on cessation of this drug.

Interpretation: The shift in utilization from rosiglitazone to insulin and sulfonylureas and the modest increase in use of pioglitazone suggest that the latter drug was not embraced as a less harmful alternative to rosiglitazone. Macrovascular comorbidities played a greater role in decisions to start or stop rosiglitazone therapy after the meta-analysis was published.

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In a meta-analysis published in late May 2007, Nissen and Wolski showed that rosiglitazone was associated with a higher rate of myocardial infarction than placebo or other glucose-lowering medications.[1] The US Food and Drug Administration (FDA) issued a related safety alert on the same day the article was published.[2] On 1 June 2007 a letter highlighting these harmful effects, issued by GlaxoSmithKline and reviewed by Health Canada, was sent to health professionals in Canada.[3] Rosiglitazone (Avandia) is 1 of 2 thiazolidinediones (TZDs) currently on the market in North America; the other is pioglitazone (Actos). Combination products include rosiglitazone–metformin, marketed as Avandamet. Recently published findings have indicated that rosiglitazone use has declined sharply since the release of the Nissen and Wolski findings.[4–6] More specifically, an analysis of elderly patients in Ontario showed that new use of rosiglitazone dropped abruptly following publication of the meta-analysis,[4] and a drug utilization study in a private insurance plan setting indicated that prevalent use of rosiglitazone by members of the plan fell by close to half from 20 May to 7 Dec. 2007.[5] The latter study also revealed that the percentage of rosiglitazone users with an elevated risk for a cardiovascular event declined during the same period. These studies have provided evidence that the meta-analysis affected the use of TZDs, but, importantly, they did not analyze patterns of switching from rosiglitazone to other drugs, nor did they consider the wider effects on prevalent use of other glucose-lowering medications.

We therefore undertook a study to examine the wider effects of the Nissen and Wolski meta-analysis, including its impact on patterns of prevalent and new use of glucose-lowering medications, cessation of TZDs, and switching from rosiglitazone to other medications. We also sought to identify predictors of initiation and cessation of rosiglitazone, including microvascular and macrovascular comorbidities. In this article, we describe the impact of the meta-analysis on use of glucose-lowering drugs and provide an analysis of the factors influencing utilization of rosiglitazone over time.

Methods

Study population. For this study, we focused on drug utilization in the Canadian province of British Columbia. TZDs were covered by the provincial drug plan as third-line therapies under a prior-authorization process as of 7 Nov. 2005 for rosiglitazone and pioglitazone and as of 2 Aug. 2007 for the combination drug rosiglitazone–metformin.[7,8] Before these coverage policies were implemented, TZDs had been available but had not been covered by the public drug plan.

We used linked data from provincial administrative health databases for prescription drugs (PharmaNet), physician services (Medical Services Plan) and hospital admissions (Canadian Institute for Health Information Discharge Abstracts Database). PharmaNet contains records of all medications dispensed at community pharmacies in British Columbia, and rates of underreporting and misclassification were expected to be minimal.[9] Similarly, physician services and hospital admissions data were expected to be reliable on the basis of studies comparing patient charts with administrative data in Canada.[10,11] Our study included B.C. residents of any age (about 4.3 million people in 2007). We restricted the sample to those registered under the Medical Services Plan to ensure exclusion of non-residents. In our analysis of predictors of initiation and cessation of rosiglitazone, we further limited the sample to those registered in the provincial income-based prescription drug plan (Fair PharmaCare) to ensure that we had detailed data on income for all study participants. The study covered the 36-month period from December 2004 to November 2007, which consisted of the 29 months before the Nissen and Wolski meta-analysis of rosiglitazone was published,[1] a transition month during which the study was published online (May 2007) and the 6 months after publication.

Definitions. Patients with 1 or more days' supply of a drug within a given month were considered "prevalent users" of the drug during that month. Patients whose current supply of a drug was set to expire during a given month and who did not fill another prescription for the same drug within 90 days of the end of their current supply were defined as having stopped the drug.[9,12–14] Patients for whom a drug was dispensed in the current month and for whom the drug had not been dispensed in the previous 365 days were defined as having started the drug. Patients for whom a new glucose-lowering therapy was dispensed within 30 days of stopping rosiglitazone or rosiglitazone–metformin were defined as having switched therapies.[12–14]

Interrupted time series analysis. We used an interrupted time series linear regression model[15,16] to test for changes in monthly prevalent use, treatment initiation and treatment cessation of rosiglitazone, rosiglitazone–metformin, pioglitazone, all TZDs, insulin, metformin, sulfonylureas, acarbose and repaglinide. We also used this model to test for changes in monthly switching from rosiglitazone or rosiglitazone–metformin to the other

glucose-lowering medications included in the study. The model included an intercept, a linear trend variable, a binary variable for the transition month during which the meta-analysis was published online (May 2007), level and trend variables for the period after the meta-analysis (June–November 2007), level and trend variables for the period after the prior-authorization policy for TZDs was introduced (November 2005 to November 2007), and monthly variables to control for seasonal variation. Although the same independent variables were used, separate regressions were estimated for prevalent use, treatment initiation, treatment cessation and switching and for each drug in the study. This model was also used to estimate, on the basis of trends in prevalent use before the meta-analysis was published, the "predicted" number of prevalent users of each glucose-lowering drug in the absence of the meta-analysis; these values allowed comparison with observed prevalence figures for November 2007. For more detail about the interrupted time series model, see the Appendix (online). We used SAS version 9.1 (SAS Institute, Inc., Cary, N.C.) for this and all other statistical analyses.

Predictors of initiation and cessation of rosiglitazone. We tested factors that have been hypothesized to predict initiation of rosiglitazone or rosiglitazone–metformin among patients with diabetes mellitus or to predict cessation of rosiglitazone or rosiglitazone–metformin among patients with a current prescription for these drugs. We used separate logistic regressions to estimate the influence of these factors on initiation and on cessation of rosiglitazone or rosiglitazone–metformin.[9,13] The method of generalized estimating equations was used to adjust for correlations within participants across repeated observations.[17–20]

The logistic regression model included a term for a linear time trend, binary variables for the transition period (May 2007) and the period following the meta-analysis (June–November 2007), and a binary variable for the period of B.C. PharmaCare coverage for TZDs under a prior authorization policy (November 2005 to November 2007). Binary variables were included for several of the patients' characteristics, specifically sex, age category, income level, Romano comorbidity score, presence of comorbidities (macrovascular or microvascular comorbidities or hypertension) and insulin dependence (defined as 2 or more prescriptions for insulin in the previous 6 months). The Romano comorbidity score is an index of a patient's comorbidities based on previous diagnoses the patient has received, and this was included as a variable to adjust for confounding caused by comorbidities,[9,21,22] excluding diabetes (a diagnosis assumed to be shared by all persons in the initiation and cessation analyses). The binary variables for the presence of macrovascular comorbidities, microvascular comorbidities and hypertension (coded as shown in Table 1)[23–25] were based on whether the patient had received a diagnosis in one of these categories during a physician or hospital visit in the previous 365 days. We also created interaction terms by multiplying each of the binary variables for macrovascular and microvascular comorbidities and hypertension with the binary variable for the period following the meta-analysis, to test whether the effect of these factors changed during the period after the meta-analysis was published.

Table 1: Diagnostic codes for comorbidities in analysis of predictors of rosiglitazone initiation and cessation

Comorbidity	Complex care codes*	ICD-9 codes	ICD-10 codes
Macrovascular			
Angina	NA	411, 413	I20
Cerebrovascular disease	NA	430–438	I60–I69
Congestive heart failure	H250	424–428	I50
Myocardial infarction	NA	410, 412	I21,122
Other ischemic heart disease	I250	414	I24, I25
Peripheral vascular disease	NA	443	I73
Microvascular			
Acute renal disease	V451	403, 404, 584, 586	N17
Chronic renal disease	D585	582, 583, 585–587, 589	N18
Diabetic neuropathy	NA	205.6, 337, 357	E10.4, E11.4, E12.4, E13.4, E14.4
Retinal disorder	NA	362	E10.3, E11.3, E12.3, E13.3, E14.3, H35, H36
Hypertension	NA	401–405	I10–I13, I15

ICD-9 = International Classification of Disease, 9th revision; ICD-10 = International Classification of Diseases, 10th revision; NA = not available.
*Created by the BC Ministry of Health Services to specify comorbidities that occur in association with diabetes mellitus.

Using the logistic regression model, we calculated odds ratios (ORs) and confidence intervals (CIs) to estimate the influence of each of the variables in the model on initiation and cessation of rosiglitazone and rosiglitazone–metformin. From the interaction terms described above (for macrovascular, microvascular and hypertension comorbidity variables), we calculated ORs and CIs to represent the impact of the meta-analysis in the absence and presence of each of these comorbidities and to represent the impact of these comorbidities before and after the meta-analysis. For more detail on the logistic regression model with generalized estimating equations, see the Appendix (online).

Results

Utilization trends for glucose-lowering medications. The introduction, in November 2005, of public coverage for rosiglitazone and pioglitazone under a prior-authorization policy was associated with a modest increase in overall TZD utilization, although it had a negative effect on the use of rosiglitazone–metformin (which was not publicly covered until August 2007) (Fig. 1). After the Nissen and Wolski meta-analysis was published in May 2007, the number of prevalent users of rosiglitazone and rosiglitazone–metformin declined. This trend coincided with a more modest increase in the number of pioglitazone users, which led to an overall steady decline in the prevalence of TZD therapy (Fig. 1). A comparison of predicted and observed utilization for November 2007 (Table 2) showed that rosiglitazone use was 40% (95% CI 39%–42%) lower than the predicted level of use. At the same time, the observed numbers of users of pioglitazone, insulin, sulfonylureas, acarbose and repaglinide exceeded the predicted numbers (Table 2).

In the interrupted time series analysis, we found that the rate of treatment cessation increased for rosiglitazone and rosiglitazone–metformin, but there was no statistically significant change in treatment cessation for pioglitazone. In the analysis of switching from rosiglitazone or rosiglitazone–metformin to other glucose-lowering drugs, there was a slight increase in switching to pioglitazone (1.2%, 95% CI 1.1%–1.4%), even smaller increases in switching to other medications, and no change in switching to repaglinide. Levels of treatment initiation decreased for rosiglitazone and rosiglitazone–metformin and increased for pioglitazone, insulin, metformin, sulfonylureas and acarbose (data available on request).

Predictors of initiation and cessation of rosiglitazone. A total of 305 969 patients were included in our analysis of predictors of initiation of rosiglitazone, and 17 573 patients were included in the analysis of predictors of cessation (Table 3). Following publication of the meta-analysis in 2007, patients were 75% less likely to initiate rosiglitazone or rosiglitazone–metformin (OR 0.25, 95% CI 0.21–0.29), and the relative odds of a patient stopping such therapy were more than 3 times higher (OR 3.29, 95% CI 3.01–3.61) (Table 4). The introduction of public coverage for rosiglitazone (under the prior-authorization policy), patient age, income level, Romano comorbidity score and insulin dependence also affected initiation and cessation (Table 4).

The presence of macrovascular comorbidities was an effect modifier that strengthened both the negative impact of the meta-analysis on the level of rosiglitazone initiation (OR 0.18, 95% CI 0.14–0.24) and the positive impact on cessation of this drug (OR 3.96, 95% CI 3.48–4.49) (Table 4). Similarly, the presence of macrovascular comorbidities was a borderline insignificant predictor of rosiglitazone initiation after publication of the meta-analysis (OR 0.78, 95% CI 0.59–1.02) and was a stronger predictor of treatment cessation (OR 1.36, 95% CI 1.24–1.48). The presence of microvascular comorbidities appeared to be a weaker predictor of rosiglitazone initiation after publication of the meta-analysis relative

Table 2: Comparison of observed and predicted prevalence* of glucose-lowering drugs in November 2007 (6 months after publication of meta-analysis)

Drug	Observed	Predicted estimate (95% CI)	Estimated difference	Estimated % difference (95% CI)
All TZDs	355	482 (476–487)	–127	–26 (–27 to –25)
Rosiglitazone	168	281 (274–289)	–113	–40 (–42 to –39)
ROSMET	29	46 (39–53)	–17	–37 (–45 to –26)
Pioglitazone	161	153 (148–157)	8	5 (3 to 9)
Insulin	702	685 (681–689)	17	2 (2 to 3)
Metformin	2441	2430 (2410–2450)	11	0.5 (–0.4 to 1)
Sulfonylureas	1178	1159 (1153–1166)	19	2 (1 to 2)
Acarbose	43	39 (37–40)	4	10 (8 to 16)
Repaglinide	41	39 (38–40)	2	5 (2 to 8)

CI = confidence interval, TZD = thiazolidinedione, ROSMET = rosiglitazone–metformin.
*Observed or predicted number of prevalent users per 100 000 B.C. residents registered in the B.C. Medical Services Plan.

to the period before publication (OR 1.31, 95% CI 1.02–1.69). Also, hypertension became a significant predictor of rosiglitazone cessation after publication of the meta-analysis (OR 1.10, 95% CI 1.02–1.18).

Interpretation

Publication of the meta-analysis by Nissen and Wolski[1] led to a decline in use of rosiglitazone and a corresponding rise in monthly prevalence of use of other glucose-lowering drugs, including pioglitazone, insulin and sulfonylureas. The prevalence of metformin use did not change significantly, perhaps because some patients who were taking metformin and rosiglitazone stopped both medications or because some patients experienced therapeutic failure with metformin (a common first-line therapy) before rosiglitazone was initiated. In our analysis of predictors of rosiglitazone initiation and cessation, we found that macrovascular comorbidities had a greater impact on decisions not to initiate or to stop rosiglitazone therapy after publication of the meta-analysis. The number of pioglitazone users rose only modestly, while the number of rosiglitazone users steadily declined. This combination of trends suggests that the increased risk of myocardial infarction was not sufficiently interpreted as a class effect to reduce the use of pioglitazone, but pioglitazone was not embraced as a less harmful alternative. The results of an earlier utilization study, which found that the percentage of rosiglitazone users at higher cardiovascular risk declined in the latter half of 2007, were consistent with our findings.[5] Moreover, our findings indicate that this shift in utilization resulted from changes in both starting and stopping decisions, which the previous study did not measure.

The decline in new and prevalent use of rosiglitazone and the rise in pioglitazone use documented in our study are consistent with the results of previous studies[4–6] examining the impact of the meta-analysis by Nissen and Wolski, but we have also demonstrated a link between the meta-analysis and an increase in prevalent use of insulin and sulfonylureas. This shift may have also been related to patients "switching back" to drugs they had used at some time in the previous 365 days, although our analysis would not have counted them as having started the drug or as having switched therapies in that case. These results differed from a study of Ontario people over age 65, which found no increased initiation of metformin, insulin or

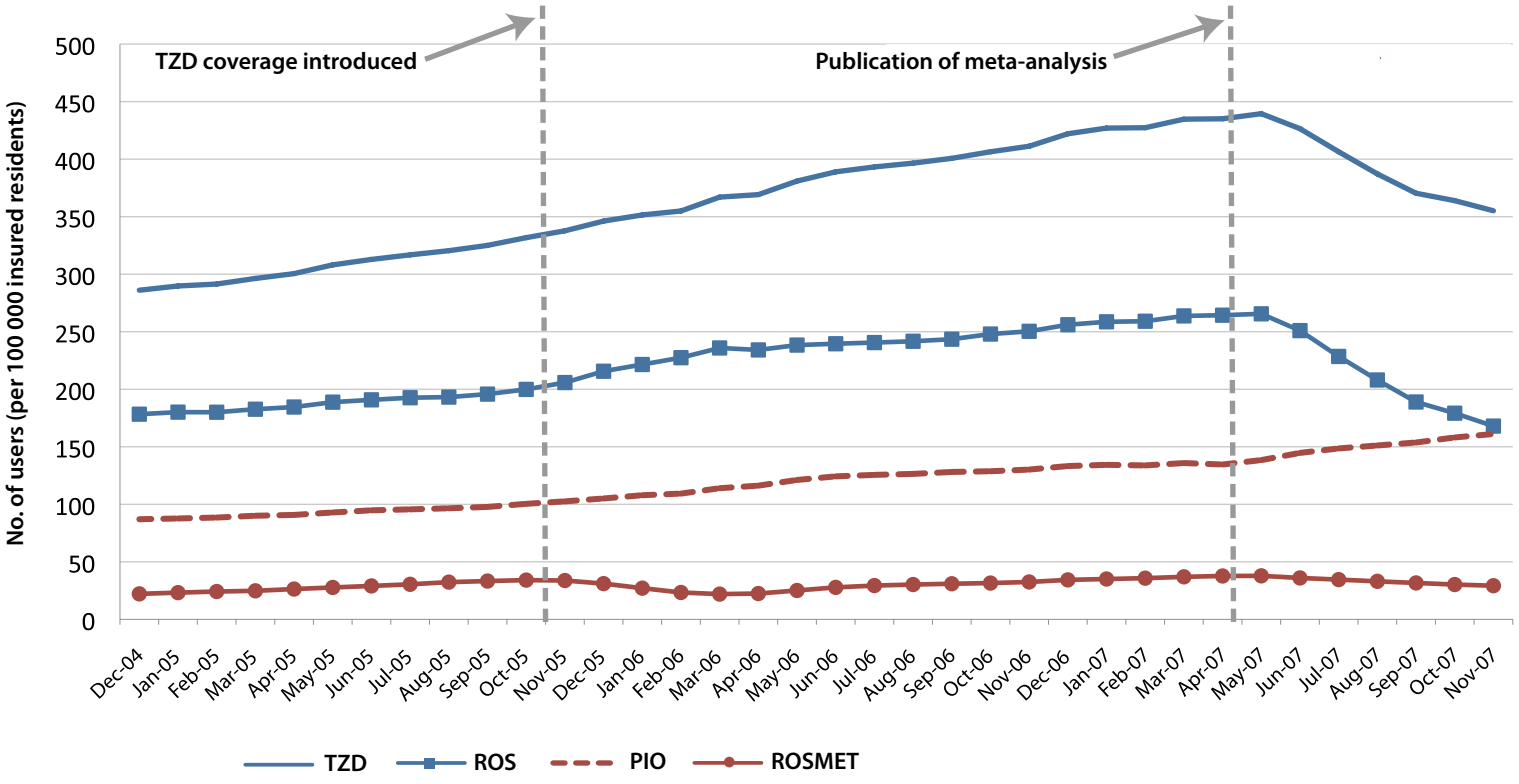

Figure 1: Monthly utilization of thiazolidinediones (TZDs) in British Columbia (per 100 000 population) before and after publication of a meta-analysis about risks associated with rosiglitazone therapy. The monthly utilization levels plotted are defined as the number of users of each medication per 100 000 BC residents registered for medical coverage in the B.C. Medical Services Plan. The dashed vertical line on the left indicates the date when public coverage was introduced for rosiglitazone and pioglitazone (7 Nov 2005), and the dashed line on the right indicates the online publication of the Nissen and Wolski meta-analysis (21 May 2007). ROS = rosiglitazone, PIO = pioglitazone, ROSMET = rosiglitazone–metformin.

glibenclamide.[4] The Ontario study raised the concern that absence of an increase in insulin initiation might indicate that patients were not receiving "an appropriate escalation in therapy."[4] By estimating changes in both new and prevalent use of glucose-lowering therapies (for a population of all ages), we were able to demonstrate not only that TZD use dropped but also that patients used other medications, including insulin, as alternatives to TZDs.

The Nissen and Wolski meta-analysis[1] has been criticized for its statistical methods, and its results cannot be considered definitive.[26,27] Nonetheless, other meta-analyses,[28] including one by the manufacturer,[29] have produced similar findings.[30] In October 2008, a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes[31,32] advised against using rosiglitazone and recommended

Table 3: Characteristics of patients included in analyses of initiation and cessation of rosiglitazone

	Type of analysis; no. (%) of patients	
Characteristic	**Initiation**	**Cessation**
Sex		
Male	153 780 (50.3)	9 995 (56.9)
Female	152 189 (49.7)	7 578 (43.1)
Age, yr		
< 40	27 738 (9.1)	507 (2.9)
40–59	96 663 (31.6)	6 809 (38.7)
60–79	145 827 (47.7)	9 086 (51.7)
≥ 80	35 741 (11.7)	1 171 (6.7)
Income, $		
< 25 000	103 288 (33.8)	4 181 (23.8)
25 000–49 999	92 799 (30.3)	5 281 (30.1)
50 000–74 999	54 125 (17.7)	3 748 (21.3)
75 000–99 999	31 696 (10.4)	2 339 (13.3)
≥ 100 000	24 061 (7.9)	2 024 (11.5)
Romano score (excluding diabetes)		
0	228 476 (74.7)	13 725 (78.1)
1	41 812 (13.7)	2 017 (11.5)
≥ 2	35 681 (11.7)	1 831 (10.4)
Comorbidities		
Macrovascular	50 820 (16.6)	2 845 (16.2)
Angina	23 389 (7.6)	1 375 (7.8)
Cerebrovascular disease	8 054 (2.6)	417 (2.4)
Congestive heart failure	14 309 (4.7)	659 (3.8)
Myocardial infarction	5 651 (1.8)	295 (1.7)
Other ischemic heart disease	17 160 (5.6)	998 (5.7)
Peripheral vascular disease	4 165 (1.4)	236 (1.3)
Microvascular	35 977 (11.8)	3 277 (18.6)
Acute renal disease	7 444 (2.4)	569 (3.2)
Chronic renal disease	7 591 (2.5)	583 (3.3)
Diabetic neuropathy	1 758 (0.6)	180 (1.0)
Retinal disorder	27 507 (9.0)	2 650 (15.1)
Hypertension	126 306 (41.3)	6 576 (37.4)
Insulin dependence		
No (< 2 insulin prescriptions in previous 6 mo)	281 225 (91.9)	16 248 (92.5)
Yes (≥ 2 insulin prescriptions in previous 6 mo)	24 744 (8.1)	1 325 (7.5)
Total no. of patients	305 969 (100.0)	17 573 (100.0)

*Data reflect patients' characteristics during the month they entered the study.

Table 4: Multivariate analysis of predictors of initiation and cessation of rosiglitazone

Characteristic	Odds ratio (95% confidence interval) Treatment initiation *n = 305 969**	Treatment cessation *n = 17 573†*
Publication of Nissen and Wolski[1] meta-analysis		
Impact in absence of measured comorbidities	0.25 (0.21–0.29)	3.29 (3.01–3.61)
Impact in presence of macrovascular comorbidities	0.18 (0.14–0.24)	3.96 (3.48–4.49)
Impact in presence of microvascular comorbidities	0.21 (0.16–0.27)	3.34 (2.96–3.76)
Impact in presence of hypertension	0.24 (0.20–0.29)	3.66 (3.30–4.07)
Impact during transition period (May 2007)	0.72 (0.62–0.83)	1.88 (1.66–2.14)
Introduction of coverage of TZDs (under prior-authorization policy)	1.12 (1.03–1.22)	1.28 (1.17–1.40)
Sex		
Male	1.00	1.00
Female	0.86 (0.83–0.90)	1.02 (0.97–1.07)
Age, yr		
< 40	1.00	1.00
40–59	2.73 (2.41–3.08)	0.63 (0.54–0.73)
60–79	2.21 (1.95–2.50)	0.60 (0.52–0.70)
≥ 80	1.30 (1.13–1.50)	0.49 (0.42–0.59)
Income, $		
< 25 000	1.00	1.00
25 000–49 999	1.05 (1.00–1.11)	0.74 (0.70–0.79)
50 000–74 999	1.13 (1.07–1.20)	0.65 (0.61–0.70)
75 000–99 999	1.20 (1.12–1.29)	0.64 (0.60–0.70)
≥ 100 000	1.21 (1.12–1.30)	0.64 (0.59–0.69)
Romano score (excluding diabetes)		
0	1.00	1.00
1	0.81 (0.76–0.87)	1.06 (1.00–1.14)
≥ 2	0.77 (0.72–0.83)	1.09 (1.01–1.17)
Comorbidities		
Macrovascular		
Before publication of meta-analysis	1.06 (0.99–1.12)	1.13 (1.05–1.21)
After publication of meta-analysis	0.78 (0.59–1.02)	1.36 (1.24–1.48)
Microvascular		
Before publication of meta-analysis	1.56 (1.47–1.65)	1.00 (0.94–1.07)
After publication of meta-analysis	1.31 (1.02–1.69)	1.01 (0.93–1.10)
Hypertension		
Before publication of meta-analysis	0.83 (0.79–0.86)	0.99 (0.94–1.04)
After publication of meta-analysis	0.80 (0.66–0.96)	1.10 (1.02–1.18)
Insulin dependence		
No (< 2 insulin prescriptions in previous 6 mo)	1.00	1.00
Yes (≥ 2 insulin prescriptions in previous 6 mo)	0.46 (0.42–0.50)	1.35 (1.25–1.45)

Note: This analysis tested initiation and cessation of treatment with rosiglitazone and rosiglitazone–metformin.
* There were 305 969 unique patients and 7 667 891 observations, with multiple observations for patients included in more than 1 monthly panel.
† There were 17 573 unique patients and 146 396 observations, with multiple observations for patients included in more than 1 monthly panel.

pioglitazone as only a third-line therapy, on the basis of existing evidence. More recently, the randomized, open-label RECORD trial compared rosiglitazone combination therapy with therapy consisting of metformin and a sulfonylurea.[33] That study was designed to investigate cardiovascular outcomes for these combination therapies, and the non-inferiority criterion was met for the trial's primary outcome of admission to hospital for cardiovascular reasons or cardiovascular death. The study showed no significant difference between the rosiglitazone and comparator groups for the predefined secondary composite outcome of cardiovascular death, myocardial infarction and stroke, but rosiglitazone use was associated with increased risk of heart failure and bone fractures. Critics of the study have suggested that the choice of primary outcome and the low event rates in the trial are weaknesses and therefore that strong conclusions cannot be drawn from the results.[34,35] Two recent observational studies suggested that pioglitazone may be a safer choice than rosiglitazone.[36,37] Neither of these observational studies reported a significant difference in risk for myocardial infarction between rosiglitazone and pioglitazone, but both reported increased risk for all-cause mortality and for heart failure with rosiglitazone.

Other safety information may have contributed to the decline in overall TZD utilization or, more specifically, to caution in the use of pioglitazone, including warnings in early 2007 in both Canada and the United States about risk of fracture,[38–41] FDA boxed warnings related to heart failure in August 2007[42] and a Health Canada endorsed advisory about rosiglitazone and cardiac safety in November 2007.[43] A limitation of our study was the inability to separately measure the effects of each warning. In our analysis of predictors of initiation and cessation of rosiglitazone, the influence of macrovascular comorbidities on utilization of this drug may have been due in part to an increase in concerns about congestive heart failure rather than only a response to the findings of Nissen and Wolski.[1] However, we can infer from the rise in the number of pioglitazone users that the decline in rosiglitazone use resulted primarily from the publication of the meta-analysis and related regulatory warnings and publicity. Our study shares a limitation with other studies of this kind in that longer-term data would be needed to show the long-term impact of the meta-analysis, although in interrupted time series analysis it becomes more difficult to attribute changes to a previous event or intervention over a longer timeframe because of other changes at the patient or population level (such as additional safety information).[14] As noted above, we probably underestimated the amount of switching from rosiglitazone or rosiglitazone–metformin to other glucose-lowering drugs, since our definition of switching did not count patients who "switched back" to a drug they had used in the past 365 days. However, changes in switching would be captured in our analysis of prevalent use of these medications. Similarly, we did not measure the number of patients who increased the dosage of a current medication to compensate for stopping rosiglitazone or rosiglitazone–metformin. Although we were able to report on the impact of the meta-analysis on trends in utilization and the modifying effect of macrovascular comorbidities on rosiglitazone utilization after publication of the meta-analysis, we did not evaluate the effects of these shifts in utilization on patients' health outcomes and cannot draw conclusions about such effects.

We found that publication of the Nissen and Wolski meta-analysis of rosiglitazone in May 2007 led to a decline in the prevalence of use of rosiglitazone and a shift toward greater use of pioglitazone and other glucose-lowering drugs, including insulin and sulfonylureas. Use of rosiglitazone therapy was influenced by a variety of factors, including demographic characteristics and health indicators. Our results provide evidence that macrovascular comorbidities played a greater role in decisions to start or stop rosiglitazone therapy as a result of the meta-analysis. Although other warnings about the safety of TZDs were issued in 2007, the findings published by Nissen and Wolski appeared to be more influential, which may relate to broader coverage in the lay and professional media[4–6] or to the perceived severity of risk of myocardial infarction relative to other safety concerns.

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